CONSIDERATIONS OF ALTERNATIVE METHODS ON TESTING PROPOSALS IN YOUR REGISTRATION

Please complete this form and provide information for each of the points below.

If you have more than one testing proposal, please copy and paste the three bullet points within the same document and complete the details as appropriate for each testing proposal.

This document will be published on ECHA website along with the third party consultation on the testing proposal(s).

Public substance name: N,N'-dimethyldiphenylthiuram disulphide
EC Number (omit if confidential): 234-196-6
CAS Number (omit if confidential): 10591-84-1

Date of considerations: 18 July 2019

- **Hazard endpoint for which vertebrate testing was proposed:**

  Sub-chronic toxicity (90-day): oral with the registered substance

- **Considerations that the general adaptation possibilities of Annex XI of the REACH Regulation were not adequate to generate the necessary information**

  - available GLP studies
    An OECD Guideline 407 study (Repeated Dose 28-Day Oral Toxicity in Rodents) in rats is available. To examine N,N'-dimethylphenylthiuram disulphide for subacute oral toxicity according to OECD TG 407 and GLP, male and female Wistar rats received doses of 0, 100, 300 and 1000 mg/kg bw/day dissolved in Solutol HS 15 / Ethanol / tap water (4 : 1 : 5) over a period of 28 days. N,N'-Dimethyldiphenylthiuram disulphide caused significant hemolytic anemia from 100 mg/kg bw/day (LOAEL) onwards increasing in severity with the dose accompanied by histopathological effects in spleen and kidney but not in the liver, discolored feces at mid and high dose rats (both sexes) and reduced body weight development in high dose rats. Dose-related increasing significant reticulocytosis can be interpreted as adaptive process. A no-observed -effect-level (NOAEL) for N,N'-dimethyldiphenylthiuram disulphide could not be established, the LOAEL is 100 mg/kg bw/day. No EOGRTS or Developmental toxicity study is available.

  - available non-GLP studies
    (no data available)

  - historical human data
    (no data available)

  - (Q)SAR
    (no reliable data available; there is no QSAR model available which is accepted by ECHA for the endpoint repeated dose toxicity)

- *in vitro* methods
  (no reliable data available; there are no in-vitro methods available which are accepted by ECHA for the endpoint repeated dose toxicity)

- weight of evidence
  (no data available; for repeated dose toxicity there is only a subacute toxicity study available: a weight of evidence consideration is therefore not feasible)

- grouping and read-across
  The QSAR Toolbox 4.3.1 has proposed 16 compounds (Empiric: Organic functional groups) for a read-across. Two of them seems suitable for a read-across due to their close structural similarity to the target compound.

  These compounds are CAS no. 41365-24-6 (N,N'-diethyl-N,N'-diphenylthio-peroxydicarbamic acid) and CAS no. 53880-86-7 (dimethyldiphenylthio-peroxydicarbamic acid).

  CAS no. 41365-24-6 has ethyl substituents instead of methyl substituents at the N-atoms.
  CAS no. 53880-86-7 has methyl substituents at the phenyl ring and no methyl substituents at the N-atoms.

  For both substances no toxicological data for repeated dose toxicity and developmental toxicity were found. Based on the absence of toxicological data for this endpoint a read-across is not possible.

  The other compounds proposed by the QSAR Toolbox 4.3.1 are structurally more different to the target compound and therefore not considered valid for a read-across. Additionally no toxicological data for these compounds are available in the QSAR Toolbox 4.3.1

- substance-tailored exposure driven testing [if applicable]
  not applicable

- [approaches in addition to above [if applicable]
  not applicable

- other reasons [if applicable]
  not applicable

- **Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable**

There is no subchronic study available as required by Regulation (EC)-1907/2006 (REACH) ANNEX IX section 8.6.2. There is a reliable short term toxicity study (28 days) available which was performed according to OECD TG 407 and GLP showing severe toxic effects which fulfill the criteria for classifying as STOT Re Category 2 according to Regulation (EC) 1272/2008 (GHS-CLP). This short term study does not provide a NOAEL but a LOAEL. Thus, an extrapolation towards a NOAEL for 90 days of treatment is uncertain. Consequently, a 90-day oral study in rats according to OECD TG 408 and GLP is proposed.

- **Hazard endpoint for which vertebrate testing was proposed:**

  Reproductive toxicity (pre-natal developmental toxicity) with the registered substance

- **Considerations that the general adaptation possibilities of Annex XI of the REACH Regulation were not adequate to generate the necessary information**

  - available GLP studies
    An OECD study according to Guideline 407 in rats (Repeated Dose 28-Day Oral Toxicity in Rodents) is available. To examine N,N'-dimethylphenylthiuram disulphide for subacute oral toxicity according to OECD TG 407 and GLP, male and female Wistar rats received 0, 100, 300 and 1000 mg/kg bw/day dissolved in Solutol HS 15 / Ethanol / tap water (4 : 1 : 5) over a period of 28 days. Survival was not affected by treatment. The only clinical observations were discolored faeces at mid and high dose rats (both sexes). Compared to controls over the period of treatment, body weight development was reduced in high dose males by 9 % and in high dose females by 12 %. For general toxicity a LOAEL of 100 mg/kg bw/day was found. No effects on reproductive organs (weights of prostate, seminal vesicle with coagulation glands, epididymides, testes, ovaries /oviducts and histopathological examination of these organs) were detected up to the highest test dose of 1000 mg/kg bw/day.

  - available non-GLP studies
    (no data available)

  - historical human data
    (no data available)

  - (Q)SAR
    (no reliable data available; there is no QSAR model available which is accepted by ECHA for the endpoint developmental toxicity)

  - *in vitro* methods
    (no reliable data available; there are no in vitro methods available which are accepted by ECHA for the endpoint developmental toxicity)

  - weight of evidence
    (no data available; for toxicity to reproduction there is only a subacute toxicity study available in which the weights of reproduction organs were determined including a histopathological examination of these organs: a weight of evidence consideration is therefore not feasible)

  - grouping and read-across
    The QSAR Toolbox 4.3.1 has proposed 16 compounds (Empiric: Organic functional groups) for a read-across. Two of them seem suitable for a read-across due to their close structural similarity to the target compound.

The compounds are CAS no. 41365-24-6 (N,N'-diethyl-N,N'-diphenylthio-peroxydicarbamic acid and CAS no. 53880-86-7 (dimethyldiphenylthio-peroxydicarbamic acid).

CAS no. 41365-24-6 has ethyl substituents instead of methyl substituents at the N-atoms.
CAS no. 53880-86-7 has methyl substituents at the phenyl ring and no methyl substituents at the N-atoms.

For both substances no toxicological data for repeated dose toxicity and developmental toxicity were found. Based on the absence of toxicological data for this endpoint a read-across is not possible.

The other compounds proposed by the QSAR Toolbox 4.3.1 are structurally more different to the target compound and therefore not considered valid for a read-across. Additionally no toxicological data for these compounds are available in the QSAR Toolbox 4.3.1

- substance-tailored exposure driven testing [if applicable]
  not applicable

- [approaches in addition to above [if applicable]
  not applicable

- other reasons [if applicable]
  not applicable

- **Considerations that the specific adaptation possibilities of Annexes VI to X (and column 2 thereof) were not applicable**

- There is no developmental toxicity study available as required by Regulation (EC)-1907/2006 (REACH) ANNEX IX section 8.7.2. The specific rules for adaption from column 1 do not apply. According to Annex IX 8.7.column 2 this study does not need to be conducted if:

  - the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or

  - the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or

  - the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure.

  - If a substance is known to cause developmental toxicity, meeting the criteria for classification as Repr Cat 1 or 2: R61 [GHS: toxic for reproduction category 1A or 1B: May damage the unborn child (H360D)], and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary.

Based on the available data none of the specific rules of Annes IX section 8.7 for adaption from column 1 do apply for N,N'-dimethyldiphenyl-thiuram disulphide (CAS 10591-84-1).

Consequently a pre-natal developmental toxicity in rats according to OECD TG 414 and GLP is proposed.